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Current Opinion in Genetics & Development

When and why are mitochondria paternally inherited?

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In contrast with nuclear genes that are passed on through both parents, mitochondrial genes are maternally inherited in most species, most of the time. The genetic conflict stemming from this transmission asymmetry is well-documented, and there is an abundance of population-genetic theory associated with it. While occasional or aberrant paternal inheritance occurs, there are only a few cases where exclusive paternal inheritance of mitochondrial genomes is the evolved state. Why this is remains poorly understood. By examining commonalities between species with exclusive paternal inheritance, we discuss what they may tell us about the evolutionary forces influencing mitochondrial inheritance patterns. We end by discussing recent technological advances that make exploring the causes and consequences of paternal inheritance feasible.

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Current Opinion in Genetics & Development 2023, **80**:102053

This review comes from a themed issue on **Evolutionary Genetics**

Edited by **Harmit Singh Malik** and **Judith Mank**

For complete overview of the section, please refer to the article collection, "Evolutionary Genetics (2023)"

Available online 26 May 2023

https://doi.org/10.1016/j.gde.2023.102053

Introduction

Mitochondria are eukaryotic organelles that contain their own genome distinct from the nuclear one. Descendant from an alpha-proteobacteria that became an endosymbiont within a proto-eukaryotic host cell, mitochondria are primarily known from their role in energy production via oxidative phosphorylation [1–4]. Unlike the nuclear genome, which usually follows a Mendelian inheritance pattern, genes in the mitochondrial genome (mtDNA) are almost exclusively inherited from the mother [5–8].

The fact that not all genes of an individual are inherited in the same way is a potent source of genetic conflict [9,10]. Uniparental inheritance means that natural selection is effective only in the sex that transmits that genetic element, which allows sexually antagonistic mutations to persist within populations. A canonical example of this conflict is cytoplasmic male sterility in plants [11–13]. In this case, maternal inheritance of the mitochondrial genome (mtDNA) results in the transmission and spread of a mtDNA mutant that induces male sterility. Subsequently, this kind of female-specific selective sieve has been dubbed 'Mother's Curse' [14,15].

Whereas maternal inheritance of mitochondrial genomes is widespread across the tree of life, it is not universal. Transmission through both sexes, either via true biparental inheritance or doubly uniparental inheritance, is restricted to a limited number of species [8]. Doubly uniparental inheritance, which is commonly observed in species of bivalvian mollusks, involves the transmission of two sex-specific mitochondrial haplotypes, one transmitted through eggs and one through sperm [16–19]. While males may retain both haplotypes, each sex only transmits its associated mitochondrial haplotype functionally resulting in uniparental inheritance. Exclusive paternal inheritance of the mitochondrial genome (as opposed to occasional paternal leakage) is even more rare, such that little theory or experimental evidence exists to explain why these species, and only these species, have evolved this unique inheritance pattern and how this (potential) mitonuclear conflict manifests.

Here, we first review explanations for why mitochondria are uniparentally inherited in general, and maternally inherited in particular. Next, we explore known examples of paternal inheritance of mitochondrial genomes and discuss their features in light of current hypotheses about their evolutionary origins. We end by suggesting some open questions and directions for future research.

Why uniparental inheritance?

Uniparental inheritance of organellar genomes relies on the presence of different mating types and sexes, such that one mating type predictably transmits the organellar genomes to its offspring relative to the other. Exclusive uniparental inheritance of organellar genomes is thought to be costly, as it excludes organelles from sexual recombination [20]. Because recombination alleviates the effects of Muller's ratchet, the irreversible accumulation

of deleterious mutations, organellar genomes tend to accumulate mutations faster than the nuclear genome, raising concerns about organellar genome stability and host population fitness [21–23]. In general, germline bottlenecks and programmed destruction of dysfunctional mitochondria with elevated mutational loads can offset some of the fitness costs associated with mutation accumulation caused by the lack of recombination [24–28], but there appears to be a cost associated with uniparental inheritance of organellar genomes that must be managed.

Why, then, has uniparental inheritance of the mitochondrial genome become near-universal across eukaryotes? Taking an explicit gene's-eye view of the question [29], Cosmides and Tooby [5] made a crucial theoretical intervention when they argued that uniparental inheritance of cytoplasmic genes could mitigate intragenomic conflict between competing mtDNAs. If mitochondria are transmitted through both parents, a 'selfish' mitochondrial mutation that is superior in terms of replication will spread through the population despite reducing organismal fitness, analogous to a sexually transmitted parasite. Under uniparental inheritance, however, such a mutation will be limited to a single lineage restricting the selfish mutation to a subset of the organismal population. Group selection against this less-fit lineage will consequently purge this 'selfish' mutation. Several mathematical extensions of this argument have since been developed, and, collectively they show that nuclear regulators that restrict the inheritance of organellar genomes to one mating type will be favored by selection ([30–33], see [34] for a review). By now, conflict avoidance is the dominant theory for the evolution of uniparental inheritance, but other alternative explanations have emphasized the role of mitonuclear co-adaptation and avoiding negative epistatic interactions between genomes [35–37].

Why maternal inheritance?

If the dominance of uniparental inheritance is well accounted for by population-genetic theory, it is less clear why it is almost exclusively maternal rather than paternal. Some hints come from the differences between genetic transmission in males and females.

The exact copy number of mitochondrial genomes per cell varies across cell types, and between the sexes [38,39]. Intense germline bottlenecks increase cell-to-cell variance in the ratio of wild-type to mutant mtDNA copies, consequently increasing purifying selection against less-fit mitochondrial haplotypes and offsetting the effect of Muller's ratchet [23,40–44]. While the magnitude of this reduction in copy number varies between species, the copy number is often several orders of magnitude greater in females than in males. In mammals, for example, mature oocytes often have mtDNA copy numbers several orders of magnitude greater than in sperm [45–49]. It is unclear how copy number differs, both for mitochondria and plastids, across plant species, but, as the larger size of the egg is suspected to contribute to differences in copy number, it is not unreasonable to assume an elevated organellar copy number in eggs relative to pollen. Organellar mutation rates in sperm and pollen are also elevated relative to egg cells, potentially due to higher oxidative damage in male gametes [50,51]. Differences in organellar germline bottleneck size and mutation rate are therefore good candidate explanations for the establishment of maternal inheritance, but this is based on a limited number of empirical studies, and it remains unclear why maternal inheritance of organellar genomes has come to dominate across eukaryotes.

Reported examples of paternal inheritance

Another way to approach the question of why maternal inheritance of mtDNA has become so ubiquitous is to ask why paternal inheritance should be so rare. Exclusive paternal inheritance of mitochondrial genomes has evolved in only a handful of species. Known confirmed examples include cucumber, melon, banana, and coast redwood (Table 1). It is important to distinguish between inheritance modes that are the evolved, stable, state as opposed to inheritance events caused by dysfunction or interspecific interactions. Occasional transmission of paternal organelles, often referred to as paternal leakage, occurs in many species (see Table S1 in Camus et al., 2022 [8] for a detailing of documented alternative inheritance modes). Paternal leakage may also happen during hybridization between species or diverged populations and may even be selected for to allow opportunities for sexual recombination between mitochondrial genomes [8]. The extent of paternal leakage across species ranges from incredibly rare (such as in tobacco) to so frequent that it is comparable to biparental inheritance (as is seen in crosses between *Pelargonium* cultivars) [52–54]. In all of these cases, however, maternal inheritance is the default state. Exclusive paternal uniparental inheritance, in contrast, is incredibly rare. The low number of reported cases makes it difficult to see how and why paternal inheritance has evolved in these species. Still, known examples have some things in common. Most strikingly, all documented cases of paternal transmission are in plant species (Table 1).

Plant and animal mitochondrial genomes have some distinct, but often-overlooked, differences (Figure 1). Animal mitochondrial genomes exhibit elevated point mutation rates in comparison to plant mitochondrial genomes [55–57], while plant mitochondrial genomes exhibit substantially higher rates of structural variation

Table 1

Reported examples of paternally inherited mitochondrial genomes.

Species common name	Mitochondrial genome size	Chloroplast inheritance	Refs
Cucumis sativus L. Cucumber	1685 kb	Maternal	[71,72][a]
Cucumis melo L. Melon	2460 kb	Maternal	[71,72][a]
Musa acuminata Dwarf banana	409 kb	Maternal	[82]
Sequoia sempervirens D. Don Endl. Coastal redwood	Unknown	Paternal	[83]

[a] Indicates whether an assembled mitochondrial genome exists for that species.

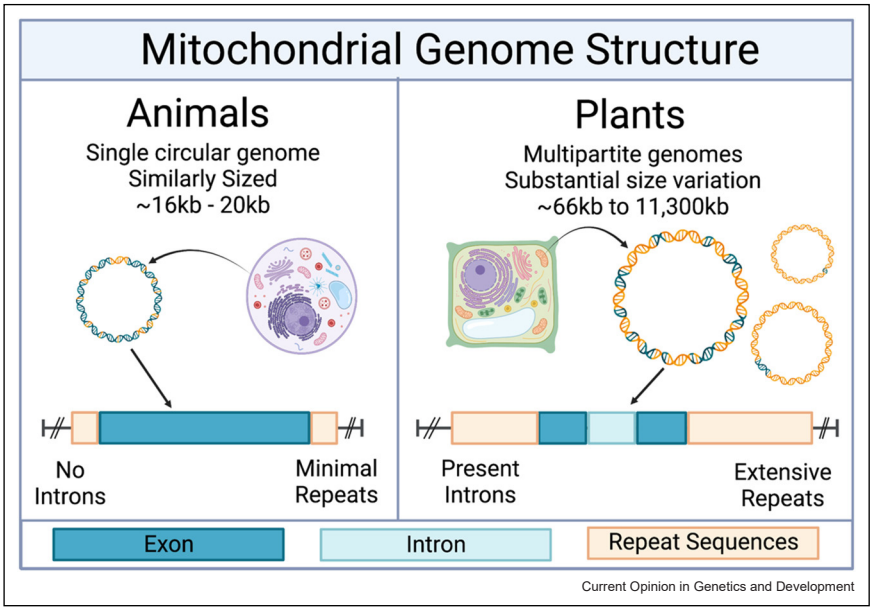
[58] (Figure 1). Whereas most animal mitochondrial genomes are small (usually around 20 kb), there is dramatic size variation across plant mitochondrial genomes. For example, the mitochondrial genome of the parasitic mistletoe, *Viscum scurruloideum*, is around 66 kb, whereas that of *Silene conica* is over 11 Mb [59,60]. Land plants (average of ~395 kb) tend to have larger mitochondrial genomes than green algae (~57 kb) [58], and variation in plant mitochondrial genome size is primarily driven by differences in

noncoding regions and species differ in the number of duplications and insertions of plastid DNA introduced via horizontal gene transfer [61–63] and in the number of introns (that are usually absent entirely in animal mitochondrial genomes) [64,65].

Expansions of repetitive sequences within plant mitochondrial genomes also affect genome architecture [66,67]. They often mediate within and between mtDNA molecule recombination, further contributing to the highly variable structure of plant mitochondrial genomes [68–70]. Such recombination may lead to the partitioning of the

entire genetic content of the mitochondrial genome into multiple subgenomic circular molecules [75–77]. Multipartite or multichromosomal mitochondrial genomes have been detected in several plant species and are likely key to the extensive variation in mitochondrial genome size and structure across plant species [58,78–81]. Consequently, while sequence divergence between plant mitochondrial genes is limited, there is

Figure 1



Visual schematic of key differences between animal and plant mitochondrial genomes. Animal mitochondrial genomes (left panel) are of smaller size with minimal variation between species, show no-to-limited intron presence, and minimal repetitive sequence content. Plant mitochondrial genomes (right panel) show substantial size variation between species, may be split into multipartite chromosomes, often have introns within genes, and may have large arrays of repetitive sequence. Mutational processes also differ between plants and animals. In plants, which contain both mitochondria and plastids, mitochondria overall exhibit reduced silent substation rates relative to both the plastid and nuclear genomes [55,71]. In contrast, across animal species, differences between mitochondrial and nuclear mutation rates are much more variable, but the mitochondrial point mutation rate generally appears to be higher [72,73]. Note that while plant mitochondrial genomes are often depicted as circles, there is evidence that this is a consequence of how they are sequenced and assembled, rather than a reflection of their physical structure [74]. Created with BioRender.com.

extensive variation in mitochondrial genome size and structure across plant species.

Why paternal inheritance?

What, then, can we learn about the evolution of paternal inheritance from the handful of documented cases? One hypothesis centers on genome instability and the role of genome size and recombination [83]. As repetitive DNA accumulates in the mitochondrial genome, the frequency of intra- and intermolecular recombination events between mitochondrial DNA increases. These recombination events can generate novel structural rearrangements affecting mitochondrial gene expression, which in turn may have a negative effect on mitochondrial function [84]. Consequently, Havey argued paternal transmission may have been selected for as it induces a more severe germline bottleneck increasing the efficacy of selection against dysfunctional mitochondria [83]. Consistent with this hypothesis, cucumber and melon have very large, repeat-rich, multipartite mitochondrial genomes.

The distribution of fitness effects for deleterious mutations is complex and varies across classes of mutations. Point mutations will usually have smaller effects than structural variants (although we lack rigorous tests of this), and this may explain why excessive structural rearrangements may necessitate tighter germline bottlenecks, than do point mutations [85]. Paternal inheritance, in these species, could consequently induce purifying selection against pollen carrying elevated numbers of dysfunctional mitochondrial DNA.

While paternal inheritance could feasibly increase purifying selection against large, unstable mitochondrial genomes, it is unclear whether this is the cause of paternal inheritance or a consequence. The largest plant mitochondrial genome ever documented is in *Silene conica* (11,300 kb), and it is rife with repetitive sequences, expanded intergenic sequences, and has fragmented into dozens of chromosomes [59]. Yet, *S. conica* not only has maternal inheritance of the mitochondrial genome but also exhibits a substantial reduction in recombination activity [59]. This directly conflicts with Havey's hypothesis, as he has also noted [83]. A recent study found that *S. conica* has greatly reduced mtDNA copy number in comparison to two closely related species [86]. Greatly reduced mtDNA copy number could serve the same purpose as paternal inheritance, functionally increasing the strength of purifying selection on the mitochondrial genome. This suggests that, while paternal inheritance of mtDNA could facilitate mitogenome expansion, it may not be required.

Finally, an alternative hypothesis is that paternal inheritance evolved by drift. If low levels of paternal leakage routinely occur or even increase in frequency during stress, as was recently demonstrated by Chung et al. (2023), the emergence of mutations in variants that enforce maternal inheritance, either by blocking the transmission of or by actively degrading paternal mtDNA, could allow for periods of biparental inheritance or even the establishment of paternal inheritance [87].

What about plastids?

Plastids perform several specialized functions, including photosynthesis, pigment production and storage, and gravitropism signaling [88]. Plastid genomes are also near-universally maternally transmitted, but there are a handful of cases where paternal inheritance has been observed. Examples include species of wild carrots [89,90] and pine [91–95]. In particular, known estimates of plastid genome size across these species are comparatively small (~120 –150 kb) [96–99]. Examining the properties of these paternally inherited genomes further weakens the hypothesis that genome size drives the evolution of paternal inheritance.

Future directions

The complex and repetitive structure of plant mitochondrial genomes has made traditional explorations of their evolution complicated. They are difficult to assemble, meaning that they are often excluded from published plant genome assemblies. In 2019, it was estimated that, in plants, only one mitogenome was published for every four nuclear genomes [100]. Out of the four well-characterized examples of paternal mitochondrial inheritance, only 2 (cucumber and melon) have an assembled mitochondrial genome. Addressing this imbalance will be crucial to understanding the origin and evolution of paternal inheritance. Recent advances in long-read sequencing technology have contributed to a substantial increase in the number of assembled plant mitogenomes in the last few years [101–107].

Technology may also help in other ways. It is now possible to transform or edit chloroplast genomes in dicots, with similar approaches being developed for mitochondrial genomes [108,109]. For example, in 2023, Chung et al. generated transplastomic tobacco lines with chloroplasts containing an antibiotic resistance marker gene and reporter *gfp* [87]. This allowed them to quantify not only the extent of paternal leakage of chloroplast DNA but also to show that it increased under mild chilling stress during male gametogenesis. These results highlight the potential of this technology to probe whether paternal inheritance evolves through an intermediate inheritance mode, such as biparental or doubly uniparental inheritance, and how potential genetic and sexual conflict is resolved throughout this transition.

A favorable system to explore the evolution of paternal inheritance is the Cucurbits. Of Cucurbitaceae,

cucumber (*Cucumis sativus* L.) and melon (*Cucumis melo* L.) have evolved paternal inheritance of mtDNA, while sister species squash (*Cucurbita pepo* L.) and watermelon (*Citrullus lanatus* [Thunb.] Matsum. & Nakai) have retained maternal inheritance [110,111]. In all four species, the chloroplast genome is maternally inherited. Additionally, there is also substantial variation in the mitochondrial genome size across these species. [111,112]. The species with maternal inheritance (watermelon and squash) have relatively small mitochondrial genome sizes of 379 kb and 983 kb, respectively [113], while the species with paternal inheritance (cucumber and melon) have some of the largest mitochondrial genomes at 1685 kb and 2460 kb, respectively [78,114]. The expansion of mitochondrial DNA sizes in cucumber and melon is driven by the accumulation of short repetitive motifs and sequence transfers from the chloroplast genome [67,115–117]. Furthermore, the cucumber mitochondrial genome also has a multipartite structure as it can be assembled into three distinct circular chromosomes of lengths 1556 kb, 84 kb, and 45 kb [78]. These circular chromosomes vary in abundance within mitochondria, with the largest chromosome occurring at approximately twice the abundance of the other two chromosomes [78].

There is still a long way ahead to work out the evolution of paternal inheritance of organellar genomes. The Cucurbits offers a promising way to get there.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

Nothing declared.

Acknowledgements

We thank Michael Havey and Madeline Oravec for discussions about the Curcurbits, we thank Yaniv Brandvain for comments on an earlier draft of the paper. Comments from the editor and two anonymous reviewers further improved the text. This work was supported by a grant from Wenner-Gren Stiftelserna/The Wenner-Gren Foundations (WGF2018-0083) to JAÅ and by a grant from the National Science Foundation Postdoctoral Research Fellowship in Biology (Grant NO. IOS-2010908) to MM.

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